

TABLE 19.—Autopsy studies of atherosclerosis (cont.)
(Figures in parentheses are number of individuals in that smoking category)¹
[SM = smokers NS = nonsmokers]

| Author, year, country, reference | Autopsy population | Data collection | Cigarettes per day | Conclusions | Comments |
|--|---|--|--|--|--|
| Viel et al., 1968 Chile (200) | 1,150 males and 290 females who died violently in 1961-1964. Smoking infor- mation avail- able only on 666 males. | Interview with relatives. | The results concerning internal fibrous streaks and fatty plaques in the left anterior descending coronary artery are reported in graphic form only. An examination of this data indicates that the moderate and heavy smokers appeared to show consistently higher percentages of diseased areas than the nonsmokers. But the statement of the authors implies that these differences were not statistically significant when subjected to an analysis of variance. | The authors conclude that: "No relationship between atherosclerotic lesions and the use of tobacco was discernible." | |
| Strong et al., 1969 U.S.A. (182) | 747 males 20- 64 years of age autopsied between 1963- 1966 at Charity Hospital in New Orleans. | Interview with next of kin within 8 weeks of death. | <i>Basal Group (excluding diseases related to smoking or CHD). Mean percentage of coronary artery internal surface involved with raised lesions (number of cases).</i> <i>White</i> NS 2 (5) 19 (14) 20 (6) 30 (11) 1-24 cigarettes/day 9 (14) 17 (10) 26 (16) 39 (7) >25 cigarettes/day 12 (9) 31 (14) 26 (25) 39 (20) <i>Negro</i> NS 4 (14) 3 (8) 16 (11) 17 (14) 1-24 cigarettes/day 3 (39) 11 (31) 14 (30) 28 (22) >25 cigarettes/day 17 (10) 14 (17) 29 (12) 16 (11) | The authors conclude that: "Atherosclerotic involvement of aorta and coronary arteries is greatest in heavy smokers and least in nonsmokers." | This report concerns only ages 26-64. No data on statistical significance provided. |

¹ Unless otherwise specified, disparities between the total number of individuals and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

severity of aortic atherosclerosis, as measured both by intensity and duration, increased with increasing use of cigarettes and that this dose-relationship persisted when the patients were matched for the consumption of alcohol. On the other hand, Viel, et al. (200) concluded from their study of accidental deaths in Chile that "no relationship between atherosclerotic lesions and the use of tobacco was discernible." Examination of the data (provided in graph form only) indicates that heavy smokers showed consistently higher percentages of diseased areas than nonsmokers, but apparently these differences were not statistically significant when subjected to an analysis of variance.

Thus, in addition to the acute effects which smoking exerts on cardiovascular physiology, cigarette smoking is associated with a significant increase in atherosclerosis.

EXPERIMENTAL STUDIES CONCERNING THE RELATIONSHIP OF CORONARY HEART DISEASE AND SMOKING

Several areas of interest in cardiovascular pathophysiology have been investigated in the search for the mechanisms by which cigarette smoking contributes to cardiovascular disease, particularly coronary artery disease. Previous Public Health Service Reviews (191, 192, 193, 198) have described in detail and commented on the results of experiments by many teams of researchers.

Central to the discussion which follows is a concept of cardiac physiology which provides a framework for analysis and understanding of the varied research. That concept concerns the dynamic balance between myocardial oxygen need and supply.

CARDIOVASCULAR EFFECTS OF CIGARETTE SMOKE AND NICOTINE

The inhalation of tobacco smoke or the parenteral administration of nicotine has been found by many researchers to be associated with a number of specific acute cardiovascular responses. These responses have been observed in human as well as animal subjects; including increased heart rate, blood pressure, cardiac output, stroke volume, velocity of contraction, myocardial contractile force, myocardial oxygen consumption, arrhythmia formation, and electrocardiographic or ballistocardiographic changes (tables A 20 to A 22). The effect of these responses on coronary blood flow will be discussed in a following section.

That the acute effects observed following the inhalation of cigarette smoke are due primarily to the nicotine present in the smoke may be seen in the results of a number of experiments. In humans, Irving and Yamamota (89) and Von Ahn (202) duplicated the

effects of cigarette smoking by the administration of nicotine intravenously. Similar results in animals were noted by Kien and Sherrod (112).

The mechanism by which cigarette smoke and hence nicotine induces these changes has been of interest to numerous investigators. Nicotine has long been known as a stimulator of both sympathetic and parasympathetic ganglia. Research has centered, therefore, on the function of catecholamines, mainly epinephrine and norepinephrine, as mediators, of these responses. Using isolated rabbit atrial myocardium, Burn and Rand (35) noted that the prior administration of reserpine to the perfusate blocked the increased rate and amplitude of contraction seen following the administration of nicotine. West, et al. (208) showed that the *in vivo* cardiac stimulating effect of nicotine was blocked by tetraethylammonium chloride. Leaders and Long (125), Romero and Talesnik (156), and, more recently, Ross and Blesa (160) have all demonstrated this blockade in animals using agents such as pentolinium, hexamethonium, guanethidine, and reserpine.

More direct evidence of the catecholamine-releasing effect of nicotine has been found by Watts (203) and Westfall, et al. (209, 210, 211) (table A22). Among animal subjects, nicotine administration and the inhalation of the smoke of standard cigarettes caused significant increases in peripheral arterial epinephrine levels, while cornsilk cigarette smoke inhalation evoked no such change. In humans, cigarette smoking was found to be associated with a significant increase in urinary epinephrine excretion.

The source of these nicotine-released catecholamines, particularly those which mediate the immediate and local cardiac responses to intracoronary injections of nicotine, is felt to be the myocardial chromaffin tissue (35, 160). The more widespread effects are most probably mediated by hormones released from the adrenal gland.

According to recent research of Saphir and Rapaport, catecholamine release may not be the sole mediator of these responses (166). These investigators reported that intra-arterial injections of nicotine into the mesenteric circulation of cats were followed within 1 to 2 seconds by enhanced myocardial performance, increased left ventricular systolic pressure, and increased systemic resistance. Sectioning of the mesenteric afferent nerves led to a diminished response. The authors concluded that the cardiovascular response to nicotine may also be neurogenic in nature. Nadeau and James (142) injected nicotine directly into the sinus node artery of dogs and noted an initial bradycardia, due probably to direct vagal stimulation, followed by tachycardia, due probably to catecholamine release.

That the presence of nicotine may predispose the myocardium, particularly a hypoxic or previously damaged myocardium, to arrhythmia formation is suggested by the research of Balazs, et al. (16), Bellet, et al. (21), and Greenspan, et al. (74). Balazs produced myocardial lesions in dogs either by pretreatment with isoproterenol or ligation of the anterior descending coronary artery. It was found that while normal animals did not develop arrhythmias upon challenge with small doses of intravenous nicotine, the animals with damaged myocardiums responded with increased arrhythmia formation shortly after their spontaneous arrhythmias had ceased. More recently, Bellet, et al. (20) studied the effect of cigarette smoke inhalation on the ventricular fibrillation threshold in anesthetized dogs. They observed a statistically significant decrease in the threshold following smoke inhalation. Greenspan, et al. (74), using isolated dog right ventricular myocardium, observed that nicotine perfusion increased the automaticity of the Purkinje fibers system and decreased the conduction velocity. The authors consider that these two nicotine-induced effects probably predispose the myocardium to the initiation of arrhythmias.

CORONARY BLOOD FLOW

Studies in animals and humans (tables A20, A21) have noted alterations in coronary blood flow (CBF) following the inhalation of cigarette smoke or the administration of nicotine. Generally, exposure of the normal subject to these agents results in an increase in flow. Kien and Sherrod (112), Leb, et al. (126), Ross and Blesa (160), Travell, et al. (189), and West et al. (208), working with normal animals, and Barger, et al. (17), working with normal humans, have demonstrated this response. As with the other cardiac responses to the administration of nicotine, it has been found that the augmentation in CBF is most probably due to the release of catecholamines. Using instantaneous coronary arterial flow measurement in dogs, Ross and Blesa (160) were able to reproduce the effects of intracoronary nicotine with the administration of epinephrine and were able to block the response to nicotine by pretreatment with pentolinium.

The direct action of catecholamines on the coronary arteries may not, however, be solely responsible for the increase in CBF seen with cigarette smoking and intravenous nicotine administration. It appears that the catecholamine-induced increase in myocardial work and therefore in myocardial oxygen requirement is a prerequisite for the increase in CBF. Kien and Sherrod (112), using tracheostomized dogs, found that without blood pressure and cardiac output changes CBF did not increase following either the inhalation of cigarette smoke or the administration of nicotine.

intravenously, although CBF did increase following such changes. Recent work by Leb, et al. (126) has utilized Rb^{86} as a radioactive marker in order to distinguish capillary flow from overall total CBF. The authors consider that this capillary flow represents that portion of CBF which is effectively involved in nutrient and oxygen exchange. The researchers observed that the increase in effective coronary flow was almost proportional to the nicotine-induced increase in myocardial oxygen consumption. However, the increase in total coronary flow which may be due to increased myocardial shunting was far in excess. Thus, the increased work evoked by the effect of nicotine on the myocardium may induce local hormonal release in the myocardium and coronary vessels leading to coronary vasodilatation and increased CBF.

This homeostatic response to increased work appears to be fully effective only in the subjects with normal coronary arteries. Bellet, et al. (22), working with normal dogs and dogs that had undergone either coronary artery ligation or artificially-induced coronary artery narrowing, noted that the increase in CBF following the intravenous administration of nicotine was significantly less among the animals with coronary insufficiency. Work with humans discussed above has revealed a similar increase in CBF with smoking in normals. Regan, et al. (154) studied seven men with EKG-proven myocardial infarction and observed that cigarette smoke evoked slight increases in myocardial oxygen consumption in only three patients and caused no overall rise in CBF. A number of other investigators have noted that patients with overt CHD do not respond to the stimulus of cigarette smoke as readily as do normals (67, 149, 164).

Thus, patients with compromised coronary circulation may not be capable of increasing their coronary flow in the face of the increased demands of a myocardium stimulated by nicotine or cigarette smoke. In the normal state, the heart responds to increased oxygen demands by increasing coronary flow because even at rest oxygen extraction is almost at a maximal level. Any further increase in extraction may produce coronary sinus pO_2 values incompatible with proper tissue oxygenation.

CARDIOVASCULAR EFFECTS OF CARBON MONOXIDE

Carbon monoxide (CO) is a colorless and odorless gas, low levels of which have significant effects on human and animal physiology which are just now beginning to be understood. According to Wynder and Hoffmann (215), it is present in cigarette smoke in concentrations of approximately 2.9 to 5.1 percent. The concentration of CO in smoke is subject to many factors, among them

the type of tobacco and the porosity of cigarette paper. The concentration of CO in smoke has been found to increase significantly toward the last puffs of the cigarette.

According to Chevalier, et al. (41), a concentration of approximately 4 percent CO in cigarette smoke will produce alveolar levels of around 0.04 percent which, equilibrated with hemoglobin, result in carboxyhemoglobin (COHb) concentrations of from 3 to 10 percent. A number of investigators have compared COHb levels in smokers and nonsmokers. Goldsmith and Landaw (73) reported the analysis of expired air samples obtained from 3,311 longshoremen. Using a regression analysis, they calculated the concentration of COHb and found that nonsmokers showed levels of 1.2 percent while those smoking over 2 packs per day had levels of 6.8 percent and that smokers of lesser amounts had intermediate levels. Occupational exposure accounted for the mean nonsmokers' level being over 1.0 percent, an unusual finding in comparison with other studies. Kjeldsen (113) interviewed and obtained blood samples from 934 CHD-free smokers and nonsmokers. The mean COHb level for 196 nonsmokers was 0.4 percent while all inhaling smokers had a mean level of 7.3 percent. All 416 cigarette smokers, regardless of inhalation or amount smoked, showed a mean level of 4.0 percent.

Carbon monoxide has many varied and significant effects on human physiology. An overall review of these effects may be found in a discussion by Lilienthal (127) or more recently in an extensive review by the United States Public Health Service National Air Pollution Control Administration (194). Apart from its effects on respiratory and circulatory function, CO has been found to affect certain central nervous system functions adversely. These effects are probably due to interference by CO with the proper oxygenation and oxidative metabolism of the tissue in question.

CO interferes with oxygen transport in a variety of ways. First, the affinity of hemoglobin for CO is approximately 200 times greater than its affinity for oxygen, and thus CO can easily displace oxygen from hemoglobin. Second, CO shifts the oxyhemoglobin dissociation curve. By increasing the avidity with which oxygen is bound by hemoglobin, CO interferes with O₂ release at the tissue level. This is of greatest importance at the tissue level where the oxygen content of the capillary blood has been reduced to approximately 40 percent saturation. Here the shift can substantially decrease the oxygen tension supplying the tissues.

Third, and of more recent note, is the possible interference by CO with the homeostatic mechanism by which 2, 3-diphosphoglycerate (2, 3-DPG) controls the affinity of hemoglobin for oxygen. Bunn and Jandl (34) have recently reviewed the various experi-

ments concerning this glycolytic intermediate. The question of whether the low levels of CO present in the blood of smokers can affect this homeostasis is presently under investigation (29, 143), and firm conclusions cannot be drawn at this time.

Apart from its effect on hemoglobin affinity, CO appears to induce arterial hypoxemia, and this may act as an additional cause of tissue hypoxia. Ayres, et al. (14, 15) observed unexpectedly that exposure of individuals to CO sufficient to raise their levels of COHb to between 5 and 10 percent was associated with a significant fall in arterial pO_2 . Greater fall in venous pO_2 was noted, but this was considered secondary to increased tissue extraction. In a recent article, Brody and Coburn (30) suggested that this COHb-induced arterial hypoxemia was due to the interaction of a number of factors. These authors noted that in the presence of veno-arterial shunts or of an imbalance in the ventilation-perfusion ratio, the shift in the oxyhemoglobin dissociation curve increased the alveolar-arterial O_2 gradient and resulted in arterial hypoxemia. The presence of shunts as small as 2 percent of cardiac output as well as of approximately 10 percent COHb was found to cause an increase in the gradient. Such ventilation-perfusion (V/Q) abnormalities have recently been noted even in asymptomatic smokers (see Chapter on Chronic Obstructive Bronchopulmonary Disease). The increased levels of COHb found in the blood of smokers may interact with these V/Q abnormalities to further decrease available oxygen.

In normal individuals, coronary flow can increase to meet the increased oxygen demands of a stressed myocardium (as that under nicotine stimulation), while in individuals with severe CHD coronary flow cannot respond as readily. In such cases, myocardial oxygen extraction must be increased above the almost maximal extraction found at rest. Any interference with arterial oxygen levels or hemoglobin affinity could very well decrease available oxygen supplies below the level required for proper tissue function. That this occurs is suggested by the experiments discussed below.

Chevalier, et al. (41) exposed 10 young nonsmokers to CO concentrations sufficient to induce COHb levels of approximately 4 percent. Taking measurements from blood specimens obtained at cardiac catheterization under resting and exercise conditions, the authors noted that the ratio of oxygen debt to oxygen uptake increased significantly under conditions of increased COHb. According to the investigators this implied that the same work was being done at a greater metabolic cost. These same authors (121, 122) had previously noted similar findings among smokers and observed

that cessation of smoking was associated with a significant improvement in oxygen debt accumulation.

More recent work by Ayres, et al. (15) has focused on the difference in response to CO exposure between 7 normals and 4 patients suffering from CHD (proven arteriographically). The induction of a COHb concentration of approximately 9 percent in the normals was followed by an increase in coronary blood flow, a decrease in hemoglobin-oxygen percent extraction and no change in myocardial oxygen consumption, coronary sinus oxygen tension, and lactate and pyruvate extraction ratios. The induction of similar COHb levels in the CHD patients was followed by no change in coronary blood flow, a decrease in the hemoglobin-oxygen extraction ratio, and no change in myocardial oxygen consumption. However, these patients did manifest a decrease in coronary sinus pO_2 as well as a decrease in lactate and pyruvate extraction. The latter measures indicate that the myocardium was functioning under hypoxic conditions. Because the coronary flow could not increase and because the myocardium could not extract O_2 from HbO_2 , which was under the influence of CO, coronary sinus oxygen tension decreased to a point which could inactivate certain oxidative enzyme processes. Thus, the myocardial function of persons with CHD may be unable to compensate for the stresses induced by smoking.

Although COHb levels resulting from the CO present in the atmosphere during periods of high air pollution are much lower than those due to the inhalation of cigarette smoke, these concentrations of COHb might contribute to the manifestations of CHD. Cohen, et al. (44) studied the case fatality rates for patients admitted to 35 Los Angeles area hospitals with myocardial infarction in relation to atmospheric CO pollution. The authors observed an increased MI case fatality rate in areas of increased pollution, and then only during periods of relatively increased CO pollution.

An area of interest which has been discussed in previous reports concerns the presence of hydrogen cyanide in tobacco smoke. According to Wynder and Hoffmann (215), the amount present ranges from 11 to 32 micrograms HCN per puff. It is known that a significant amount of this material is detoxified to thiocyanate and excreted as such in the urine or saliva. However, cyanide is a potent inhibitor of oxidative metabolism. Such inhibition of myocardial oxidative metabolism may be of importance when combined with the other factors mentioned above which tend to decrease the oxygen supply available and increase the need for oxygen on the part of the myocardium.

EFFECTS OF SMOKING ON THE FORMATION OF ATHEROSCLEROTIC LESIONS

A number of autopsy studies have demonstrated a significant association between cigarette smoking and the presence of aortic and coronary artery atherosclerosis, even in men without a history of clinical CHD. The possible pathophysiologic mechanisms for the atherogenic influence of cigarette smoking are discussed in this section.

A number of investigators have studied the effect of nicotine administration, either subcutaneously or intravenously, upon atherosclerotic changes in the aorta and coronary arteries of animals (table A 23). When administered alone, nicotine induces certain necrotic changes in the arterial wall. However, in combination with the administration of increased amounts of cholesterol in the diet, nicotine aggravates either subendothelial fibrosis (75) or definite atheromatous lesions (46, 75, 80, 130, 178). Studies by Choi (42) and by Wenzel, et al. (207) did not demonstrate this synergism between cholesterol and nicotine.

The other major cigarette smoke component under discussion in this chapter, carbon monoxide, has also been recently implicated in atherogenesis. Table 24 presents the studies which have related exposure to CO in combination with increased dietary cholesterol to both macroscopic and microscopic aortic and coronary atheromatosis. Astrup, et al. (10) exposed cholesterol-fed rabbits to CO continually over a period of up to 10 weeks. The experimental group showed increased aortic atheromatosis over that shown by the control group, also cholesterol-fed. Kjeldsen, et al. (114) observed that exposure of rabbits to increased oxygen concentrations significantly reduced the amount of cholesterol-induced atheromatosis in rabbits. Most recently, Webster, et al. (204) have extended this research to primates. These investigators found that cholesterol-fed squirrel monkeys developed significantly more coronary artery atherosclerosis when exposed intermittently to CO over a 7-month period than when exposed only to room air.

Recent discussion has centered on the mechanisms whereby CO can induce these changes (9, 212). Astrup (9), referring to previous experiments in humans which had shown increased vascular permeability for albumin upon chronic exposure to CO (11), considers it likely that this increase in permeability allows for increased filtration of lipoproteins into arterial walls. This, he considers, is a primary cause of intimal and medial lipid accumulation and, therefore, of atherosclerosis.

Another point of view has been stressed by Whereat (212), who considers the filtration theory to be an inadequate hypothesis for

TABLE 24.—Experiments concerning the atherogenic effect of carbon monoxide exposure and hypoxia

| Author, year, country, reference | Number and type of animal | Procedure | Results |
|---|--------------------------------------|--|--|
| Astrup et al., 1967, Denmark (10). | 24 female albino rabbits. | Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) continual exposure to carbon monoxide: 0.017 percent for 8 weeks. 0.036 percent for 2 weeks. | The experimental group exposed to carbon monoxide showed increased macro- and microscopic aortic atheromatosis over that shown by control animals. Microscopic examination revealed intimal lipid deposition limited in penetration by the internal elastic membrane. Coronary vessels were found to show similar changes. Carboxyhemoglobin (COHb) levels averaged 15-19 percent during the first 8 weeks and 33 percent during the final 2 weeks. |
| Kjekdaen et al., 1968, Denmark (117). | 24 castrated male albino rabbits. | Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) continual exposure to hypoxia: 10 percent O_2 for 6 weeks. 9 percent O_2 for 2 weeks. | The experimental group exposed to hypoxia showed increased macroscopic aortic atheromatosis over that shown by control animals. Microscopic examination revealed more intimal and subintimal lipid deposition in the aortas of the exposed rabbits than in those of the nonexposed. The total amount of cholesterol deposited in the aortas of the experimental group was three times higher than in those of the control group. |
| Kjekdaen et al., 1969, Denmark (114). | 24 castrated male albino rabbits. | Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) exposure to 28 percent O_2 for 10 weeks. | Macroscopically, the experimental group showed significantly fewer atheromatous changes. Microscopically, the experimental group showed significantly less aortic intimal lipid deposition. |
| Webster et al., 1970, U.S.A. (204). | 22 female squirrel monkeys. | Diet containing 0.5 percent cholesterol and 25 percent fat: I. (10) control. II. (12) experimentally exposed to 200-300 p.p.m. carbon monoxide for 20 hours per week for 7 months. | The experimental group exposed to carbon monoxide showed a greater mean percentage of coronary arteries with atherosclerotic lesions and more lumen occlusion among the affected arteries. There were significantly more CO-treated monkeys than control monkeys having 35 percent or more apparent atherosclerotic stenosis among the affected arteries. Aortic atherosclerosis was apparently not aggravated by exposure to CO. COHb levels at the end of each exposure period averaged 16-26 percent during the final 24 weeks of the experiment. |

mural lipid accumulation. The author notes that when the oxidation of the pyridine nucleotide, nicotinamideadenine dinucleotide (NAD), is impaired, the reduced form of this nucleotide (NADH) provides an essential factor for fatty acid synthesis. Fatty acid synthesis in the aorta and heart is carried out by mitochondrial enzymes whose hydrogen donor is NADH. Substances which slow or impair the reoxidation of this compound tend to increase mitochondrial fatty acid synthesis (and decrease fatty acid utilization) in the arterial wall. Carbon monoxide prevents this oxidation process both directly and indirectly. Indirectly, it decreases the oxygen available for diffusion into the tissue. Directly, carbon monoxide can stall the process of NADH oxidation by combining with cytochrome oxidase. Further research is required into this problem, particularly in view of the fact that cyanide is also a respiratory chain inhibitor and thus may also adversely affect arterial wall fat metabolism.

THE EFFECT OF SMOKING ON SERUM LIPID LEVELS

In the discussion concerning the epidemiological aspects of CHD, it was noted that increased serum cholesterol was a significant risk factor for the development of overt CHD. Serum triglycerides have also been related to CHD incidence. Of concern also is the immediate effect which cigarette smoking has upon blood lipid levels.

The studies concerning this immediate effect are presented in tables A 25 and A 25a. The table is divided into a section concerning studies on humans (table A 25) and one concerning studies utilizing animals or *in vitro* systems (table A 25a). Although no consistent response was noted for serum cholesterol, serum free fatty acids were found consistently to rise following smoking. As with other cardiovascular reactions to nicotine and smoking, it appears that the fatty acid response is also mediated by catecholamine release. This relationship has been observed in a number of experiments by Kershbaum, et al. (105, 106, 108, 109, 110) and Klensch (118). That nicotine is primarily responsible for this rise may be seen by reference to the study by Kershbaum, et al. (105) in which lettuce-leaf cigarettes of minimal nicotine content had a negligible effect upon serum free fatty acids in comparison with that of regular cigarettes.

While attention has been centered upon nicotine as the agent inducing the immediate increase in serum lipids, recent studies have been concerned with the effect of chronic exposure to carbon monoxide on serum lipid metabolism. These studies are listed in table A 26. Among rabbits fed increased amounts of cholesterol,

the authors observed significant increases in cholesterol and triglyceride concentrations in those exposed to CO versus those maintained in a normal atmosphere.

THE EFFECT OF SMOKING ON THROMBOSIS

In the study of CHD, a number of investigators have turned their attention to thrombosis because myocardial infarction and sudden coronary death frequently result from thrombotic events. A thrombus may be of either gross or microscopic dimensions, and a minute thrombus at a strategic site may precipitate a fatal arrhythmia. However, thrombotic and prethrombotic states are difficult to detect except when gross, and the emphasis has been primarily on factors which can be studied conveniently. Coagulation is now thought to have a secondary role in the consolidation of an arterial thrombus and little if any in initiating the process. The prime mechanism in thrombogenesis appears to be the reaction of the platelet. Several papers have been written about platelet reactivity *in vitro* but few about the effect of smoking on platelet behavior *in vivo*. The assay of fibrinolysis, which may also be important, has received scanty treatment. The relevant studies are listed in table A27. Many of these are discussed in the 1968 supplement (192) and by Murphy (140). Corroborative data are still inconclusive as to whether smoking shortens platelet survival.

OTHER AREAS OF INVESTIGATION

Certain other aspects of cardiovascular pathophysiology may be of importance in the relationship of smoking to CHD. Glucose metabolism and insulin response, when altered, may alter myocardial response. This topic has been covered in detail in the 1968 Supplement to the Health Consequences of Smoking (192). Also, variations in blood hemoglobin and hematocrit may adversely affect coronary blood flow. A number of studies showing a possible relationship of smoking to hemoconcentration have been reviewed previously (191, 192), and the reader is referred to those discussions.

CEREBROVASCULAR DISEASE

The term cerebrovascular disease (CVD) refers to a number of different types of vascular lesions affecting the central nervous system: subarachnoid hemorrhage, cerebral hemorrhage, cerebral embolism, and thrombosis (ICD Codes 330 to 334). In 1967 in the United States, a total of 93,071 males and 109,113 females were listed as dying from CVD as the underlying cause (196).

Epidemiological studies indicate that cigarette smoking is asso-

ciated with increased mortality from cerebrovascular disease, whether CVD is listed as the underlying or as a contributory cause of death. Table 28 presents the results of the seven major epidemiological studies. The smoking of pipes and cigars does not appear to increase significantly the risk of dying from CVD. The importance of high blood pressure and diabetes as risk factors for mortality from CVD has recently been noted by Hammond and Garfinkel (76). The data from their study, as presented in table 28, also indicate that the mortality ratio for cigarette smokers is greater for persons under 75 years of age than for older individuals.

Many of the pathophysiological considerations discussed in the sections concerning CHD may also pertain to the relationship of smoking and CVD, particularly cerebral infarction.

In a study reported by Kuhn (123), 20 habitual smokers refrained from smoking for one-half day, and base line retrograde brachiocerebral angiograms were taken; they then smoked one cigarette, inhaling deeply, and had repeat angiograms. Those over 60 years of age failed to have significant acceleration of flow as demonstrated in carbon dioxide inhalation experiments.

More recently, Miyazaki (132) studied the effect of smoking on the cerebral circulation of 12 moderate/heavy cigarette smokers as measured indirectly using an ultrasonic Doppler technique to record internal carotid artery flow. Measurements were made before and after ordinary smoking and showed an increase in cerebral blood flow and a decrease in cerebral vascular resistance in all subjects. No significant difference in response was observed between the 4 younger and 8 older (over 60 years of age) subjects. More research is needed to clarify the role of cigarette smoking in the acute pathogenesis of CVD manifestations. However, the chronic effect of smoking upon the cerebral circulation (particularly its extracranial portion) is likely to be similar to the effect of smoking upon the aortic and coronary atherosclerosis.

NON-SYPHILITIC AORTIC ANEURYSM

Aortic aneurysm is an uncommon but not rare cause of death. In 1967 in the United States, a total of 8,448 men and 3,173 women were listed as dying from aortic aneurysm as the underlying cause (196). Cigarette smoking appears to increase the risk of dying from this disease, perhaps by promoting the atherosclerotic process which underlies this type of aneurysm. As illustrated in table 29, the mortality ratios for cigarette smokers are high relative to other cardiovascular diseases in which smoking increases the risk, and the risk increases in proportion to the amount smoked.

TABLE 28.—Deaths from cerebrovascular disease related to smoking

(Mortality ratios—actual number of deaths shown in parentheses)¹

[SM = smokers NS = nonsmokers]

| PROSPECTIVE STUDIES | | | | | | | |
|--|---|---|-----------------|---|--------------------|------------------|---|
| Author, year, country, reference | Number and type of population | Data collection | Follow-up years | Number of deaths due to CVD as underlying cause | Cigarettes per day | Pipes and cigars | Age variation |
| Hammond and Horn, 1958, U.S.A. (77, 78). | 187,788 white males in 9 states 50-69 years of age. | Questionnaire and follow-up of death certificate. | 8½ | 1,050 | NS |1.00 (184) | †(p<0.01). |
| | | | | | Cigarettes | | |
| | | | | | SM |†1.80 (556) | |
| | | | | | Other SM | ...1.25 (330) | |
| | | | | | Cigarettes only | | |
| | | | | | <10 |1.24 (41) | |
| | | | | | 10-20 |1.44 (140) | |
| | | | | | >20 |1.46 (83) | |
| Doll and Hill, 1964, Great Britain (80). | Approximately 41,000 male physicians. | Questionnaire and follow-up of death certificate. | 10 | 605 | NS |1.00 | |
| | | | | | All SM |1.06 | |
| | | | | | All cigarette | ...1.12 | |
| | | | | | 1-14 |1.10 | |
| | | | | | 15-24 |1.09 | |
| | | | | | >25 |1.26 | |
| Kannel et al., 1965, U.S.A. (86). | 5,127 males and females 30-59 years of age. | Medical examination and follow-up. | 12 | 13 | NS |1.00 (5) | Data apply only to males 30-59 years of age at entry. |
| | | | | | Heavy SM (>20) |3.23 (8) | |
| | | | | | | | Data apply only to cerebral infarction. |

¹ Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

TABLE 28.—Deaths from cerebrovascular disease related to smoking (cont.)

(Mortality ratios—actual number of deaths shown in parentheses)¹

[SM = smokers NS = nonsmokers]

| PROSPECTIVE STUDIES | | | | | | | |
|---|--|---|-----------------|--------------------------------------|---------------------------|---------------------------|-----------------|
| Author, year, country, reference | Number and type of population | Data collection | Follow-up years | Number of deaths due to CVD as cause | Cigarettes per day | Pipes and cigars | Age variation |
| Kahn, 1966, U.S.A. (22). | U.S. male veterans 2,285,674 person years. | Questionnaire and follow-up of death certificate. | 8½ | 2,008 | NS 1.00 (614) | Pipes | |
| | | | | | All | SM .. 1.06 (82) | |
| | | | | | current 1.80 (1,894) | NS .. 1.00 (614) | |
| | | | | | Current | Cigars | |
| | | | | | cigarettes ... 1.52 (692) | NS .. 1.00 (614) | |
| | | | | | 1-9 1.51 (98) | SM .. 1.08 (185) | |
| | | | | | 10-20 1.42 (825) | | |
| Hammond and Garfinkel, 1959, U.S.A. (76). | 858,584 males and 445,875 females 40-79 years of age at entry. | Questionnaire and follow-up of death certificate. | 6 | 4,099 | 21-39 1.70 (215) | | |
| | | | | | >39 1.59 (87) | | |
| | | | | | | Current regular cigarette | |
| | | | | | | 40-49 | Males |
| | | | | | | 50-59 | 60-69 |
| | | | | | | 70-79 | |
| | | | | | | Never | |
| | | | | | | smoked 1.00 | 1.00 1.00 1.00 |
| | | | | | | 1-9 2.79 | 1.95 1.30 0.95 |
| | | | | | | 10-19 1.14 | 1.48 †1.44 0.92 |
| | | | | | | 20-39 2.21 | 2.03 1.62 1.22 |
| | | | | | | >40 1.64 | 2.40 1.72 †0.68 |
| | | | | | | | Females |
| | | | | | | Never | |
| | | | | | | smoked 1.00 | 1.00 1.00 1.00 |
| | | | | | | 1-9 1.50 | 1.26 1.26 0.83 |
| | | | | | | 10-19 2.60 | 2.70 2.15 †0.57 |
| | | | | | | 20-39 2.90 | 2.67 1.83 1.28 |
| | | | | | | >40 †5.70 | †3.52 — — |

¹ Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

TABLE 28.—Deaths from cerebrovascular disease related to smoking (cont.)

(Mortality ratios—actual number of deaths shown in parentheses)¹

SM = Smokers.

NS = Nonsmokers.

| PROSPECTIVE STUDIES | | | | | | |
|--|---|---|----|----|--|---|
| Paffenbarger, et al. 1970 U.S.A. (144). | 3,263 male longshoremen 35-64 years of age in 1961. | Initial multi-phasic screening and follow-up of death certificate. | 16 | 67 | NS and <20 1.00 (42) >20 1.15 (25) | |
| RETROSPECTIVE STUDY | | | | | | |
| Paffenbarger and Williams 1967 U.S.A. (145). | >50,000 male University students followed up to 50 years. | Initial college entrance medical examinations with follow-up of death certificate. Controls—surviving classmates age-matched. | | | Death Rates Cases (158) Controls (618) SM 45.0 31.3 (p<0.01) Cigarette SM >10 per day . 20.9 11.2 (p<0.01) | The 63 deaths from occlusive stroke contributed to the statistical significance. The 95 deaths from hemorrhagic stroke showed no statistical significance as a single group. |

¹ Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

TABLE 29.—Deaths from nonsyphilitic aortic aneurysm related to smoking—prospective studies

(Mortality ratios—actual number of deaths shown in parentheses)¹

[SM = Smokers NS = Nonsmokers]

| Author, year, country, reference | Number and type of population | Data collection | Follow-up years | Number of deaths | Cigarettes per day | Pipes | Cigars | Comments |
|--|--|--|--------------------|------------------------|--|---------------------------------|----------------------------------|---|
| Hammond and Horn, 1958, U.S.A. (77, 78). | 187,783 white males in 9 states 50-69 years of age. | Questionnaire and follow-up of death certificate. | 3½ | 68 | NS1.00 (25) (expected) SM2.72 (68) (p<0.005) | | | |
| Kahn, 1966, U.S.A. (92). | U.S. male veterans 2,265,674 person years. | Questionnaire and follow-up of death certificate. | 8½ | 491 | NS1.00 (58) Current cigarettes5.24 (234) 1-9 cigarettes/day ...2.12 (13) 10-205.53 (124) 21-395.95 (76) >397.26 (17) | NS ..1.00 (58) SM ..1.13 (8) | NS ..1.00 (58) SM ..2.06 (24) | |
| Hammond and Garfinkel, 1969, U.S.A. (76). | 358,534 males 445,875 females 40-79 years of age at entry. | Questionnaire and follow-up of death certificate. | 6 | 337 | NS1.00 1-92.62 10-193.85 20-394.54 >408.00 | | | Data apply only to males 50-69 years of age. |
| Weir and Dunn, 1970, U.S.A. (205). | 68,153 California male workers 35-64 years of age at entry. | Questionnaire and follow-up of death certificate. | 5-8 | 51 | NS1.00 All2.64 ±102.44 ±202.88 ≥302.54 | | | SM include ex-smokers. NS include pipe and cigar smokers. |

¹ Unless otherwise specified, disparities between the total number of deaths and the sum of the individual categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

PERIPHERAL ARTERIOSCLEROSIS

Peripheral arteriosclerosis represents the effects on the vasculature of the extremities of the pathophysiologic processes which produce coronary and aortic atherosclerosis. A number of studies have been concerned with smoking as a risk factor in the development of this disease. Kannel, et al. (95) observed, in the Framingham study, that diabetes mellitus and elevated serum cholesterol, as well as cigarette smoking, were also risk factors in the development of peripheral vascular disease.

Juergens, et al. (92) reviewed the records of and contacted 478 male patients with arteriosclerosis obliterans (a severe form of peripheral arteriosclerosis), who had been patients at the Mayo Clinic between 1939 and 1948. The diagnosis of this condition was based upon certain clinical criteria: the presence of intermittent claudication, the marked diminution or absence of lower extremity arterial pulsations, and objective trophic manifestations of peripheral limb ischemia. Smoking information was available on 401 patients. These patients were compared with a control group of 350 Mayo Clinic patients of similar age who showed no clinical evidence of vascular disease. It was found, for males under the age of 60, that 2.5 percent of the cases and 25 percent of the controls were nonsmokers. However, no difference was noted between the percentages of heavy smokers in each group. The authors also implicated high blood pressure and elevated serum cholesterol as risk factors in the occurrence of this disease.

Begg (19) noted similar findings in a study of 294 male patients with intermittent claudication who were patients at the Western Infirmary in Glasgow, Scotland. In comparing the smoking histories of 100 patients with this complaint with those of 116 healthy male controls, the author found that 1 percent of the patients and 21 percent of the controls had never smoked. A total of 42 percent of the patients smoked more than 20 cigarettes per day while only 24 percent of the controls had a similar history of heavy smoking. The author concluded that smoking, while not a prime cause of peripheral arterial disease, is a significant cofactor in its development in almost all cases. The author also noted obesity, high blood pressure, and elevated serum cholesterol as risk factors.

Schwartz, et al. (168) compared the prevalence of risk factors in four groups of subjects: 141 cases with arteriosclerotic disease of the lower limbs, 551 cases with coronary arteriosclerosis, 58 cases with both conditions, and finally an indefinite number of control individuals who had been hospitalized for injuries. The investigators reported that certain risk factors, including hypercholesterolemia, hypertension, and cigarette smoking, were signifi-

cant in both coronary and lower limb arteriosclerosis. The authors noted that the inhalation of cigarette smoke appeared to be an important risk factor for coronary arteriosclerosis up to age 55 while in arteriosclerosis of the lower extremities, inhalation appeared to increase the risk even in the older age groups.

Widmer, et al. (213) compared 277 male patients with arterial occlusion of the limbs as demonstrated by aortography or oscillography with 2,082 men demonstrated by oscillography to be free of arterial disease. The authors found that cigarette smoking, particularly heavy smoking, was significantly more frequent among the cases with arterial occlusion than among the controls. Increased beta-lipoproteins and systolic hypertension were also found to be more common among the cases.

EXPERIMENTAL EVIDENCE

A number of experimenters have investigated the acute effects of smoking or nicotine upon the peripheral circulatory system. These investigators, as listed in table A 30, have measured effects in terms of alterations in skin temperature and blood flow as measured by plethysmography, radioactive iodinated albumin clearance, or radiosodium clearance from the skin. The majority of these studies have shown significant decreases in peripheral blood flow and skin temperature upon smoking, particularly in persons without manifest peripheral vascular disease. The study of Freund and Ward (68) demonstrates the difference in peripheral vascular reactivity found between normals and patients with arteriosclerotic changes in the vessels of their extremities. The work of Strömblad (181) on blockade of this response with automatic system blockers indicates that the reactivity of these vessels is secondary to the local release of catecholamines. Most probably, the degenerative changes associated with this disease create a stiffening of the vessel wall and prevent rapid alteration, particularly dilatation, in response to the catecholamines liberated by smoking or nicotine.

THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans (Buerger's Disease) (TAO) is an uncommon obstructive vasculitis primarily involving the arteries and veins of the extremities. Severely affected patients may even lose their limbs secondary to ischemic changes. Much discussion has centered upon the question as to whether this disease is a clinical and pathological entity separate from peripheral arteriosclerosis. McKusick, et al. (128) consider it to be a distinct entity

while Eisen (57) concludes that TAO is the acute inflammatory phase of severe arteriosclerosis.

Clinically, it has been shown that smoking aggravates this disease and cessation of smoking frequently aids in complete or partial remission. Razdan, et al. (153) and Brown, et al. (32) found very few nonsmokers in groups of patients diagnosed as having typical TAO. A recent study from Israel (16) involved a case-control comparison of 46 patients with TAO and 32 matched controls. Although the controls were found to smoke less per day than the patients, this difference was not found to be statistically significant. However, 100 percent of the smoking patients and only 72 percent of the smoking controls were inhalers, a difference significant at the 0.02 level.

CARDIOVASCULAR DISEASES

SUMMARY AND CONCLUSIONS

CORONARY HEART DISEASE

1. Data from numerous prospective and retrospective studies confirm the judgment that cigarette smoking is a significant risk factor contributing to the development of coronary heart disease including fatal CHD and its most severe expression, sudden and unexpected death. The risk of CHD incurred by smokers of pipes and cigars is appreciably less than that by cigarette smokers.

2. Analysis of other factors associated with CHD (high serum cholesterol, high blood pressure, and physical inactivity) shows that cigarette smoking operates independently of these other factors and can act jointly with certain of them to increase the risk of CHD appreciably.

3. There is evidence that cigarette smoking may accelerate the pathophysiological changes of pre-existing coronary heart disease and therefore contributes to sudden death from CHD.

4. Autopsy studies suggest that cigarette smoking is associated with a significant increase in atherosclerosis of the aorta and coronary arteries.

5. The cessation of smoking is associated with a decreased risk of death from CHD.

6. Experimental studies in animals and humans suggest that cigarette smoking may contribute to the development of CHD and/or its manifestations by one or more of the following mechanisms:

- a. Cigarette smoking, by contributing to the release of catecholamines, causes increased myocardial wall tension, contraction

velocity, and heart rate, and thereby increases the work of the heart and the myocardial demand for oxygen and other nutrients.

- b. Among individuals with coronary atherosclerosis, cigarette smoking appears to create an imbalance between the increased needs of the myocardium and an insufficient increase in coronary blood flow and oxygenation.
- c. Carboxyhemoglobin, formed from the inhaled carbon monoxide, diminishes the availability of oxygen to the myocardium and may also contribute to the development of atherosclerosis.
- d. The impairment of pulmonary function caused by cigarette smoking may contribute to arterial hypoxemia, thus reducing the amount of oxygen available to the myocardium.
- e. Cigarette smoking may cause an increase in platelet adhesiveness which might contribute to acute thrombus formation.

CEREBROVASCULAR DISEASE

1. Data from numerous prospective studies indicate that cigarette smoking is associated with increased mortality from cerebrovascular disease.

2. Experimental evidence concerning the relationship of smoking and cerebrovascular disease is at present insufficient to allow for conclusions concerning pathogenesis. However, some of the pathophysiological considerations discussed concerning CHD may also pertain to the relationship of smoking and CVD, particularly cerebral infarction.

NON-SYPHILITIC AORTIC ANEURYSM

Cigarette smoking has been observed to increase the risk of dying from nonsyphilitic aortic aneurysm.

PERIPHERAL VASCULAR DISEASE

1. Data from a number of retrospective studies have indicated that cigarette smoking is a likely risk factor in the development of peripheral vascular disease. Cigarette smoking also appears to be a factor in the aggravation of peripheral vascular disease.

2. Cigarette smoking has been observed to alter peripheral blood flow and peripheral vascular resistance.

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